REMARKS/ARGUMENTS

The Final Office Action dated June 18, 2008, rejected all pending claims, i.e., claims 1-3 and 5-16. No claim has been amended in this response.

This submission is proper under 37 C.F.R. § 1.114, because it presents new arguments in support of patentability that could not have been previously raised. All references cited in the Final Office Action had not been cited in any previous Office Action, and this response is the first opportunity provided to Applicants to respond to the new grounds of rejection..

The Office Action contains four different obviousness rejections under 35 U.S.C. § 103: (i) claims 1-2 and 8-10 were rejected as allegedly obvious over PCT Pub. No. WO 99/20289 to Oppenheim et al. (Oppenheim) and U.S. Patent No. 5,639,473 to Grinstaff et al. (Grinstaff); (ii) claims 1-2 and 8-14 were rejected as allegedly obvious over Oppenheim and Grinstaff in further view of Brinkhaus et al, Phytomedicine 7, 427-448 (2000) (Brinkhaus); (iii) claims 1-3 and 5-15 were rejected as allegedly obvious over Oppenheim, Grinstaff, and Brinkhaus in further view of U.S. Patent Pub. No. 2002/0165169 A1 to Kim et al. (Kim); and (iv) claims 1-3 and 5-16 were rejected as allegedly obvious over Oppenheim, Grinstaff, Brinkhaus, and Kim in further view of U.S. Patent No. 5,863,553 to Britton et al. (Britton)

Before addressing the specific rejections and the cited references, it may be helpful to briefly review the presently claimed invention.

As set forth more clearly in claim 1, the invention may relate to a therapeutic composition having the following three features: (1) The active ingredient is a mixture comprising extracts of three specific herbs (extracts of the plants *Sambucus nigra*, *Centella asiatica* and *Echinacea purpurea*); (2) The composition is in a solid form and is mucoadhesive, and therefore adheres to the mucosal tissue (in order to locally treat inflamed mucosa); and (3) The excipients combined in the composition together with the aforementioned herbs are the following: an adhesive polymer of acrylic acid, polyvinylpyrrolidone and also a bulk ingredient.

The inventors found that the combination of *Sambucus*, *Centella*, and *Echinacea* enhances adhesiveness to the mucosa, and therefore these three herbs can be formulated into a solid mucoadhesive composition which can be placed onto the mucosa to effectively accomplish the local treatment, as explained in more detail below. A preferred dosage form is the tablet of claim 2, with its specific structural features.

The Patent Office rejected the claims on the grounds of obviousness over several combinations of prior art citations. It appears that the major reference relied upon by the Patent Office is Oppenheim. Applicants believe that none of the three features of the presently claimed invention as set forth above and as arranged in the claim was taught by Oppenheim.

Regarding the first element, Oppenheim lists a large number of individual herbal extracts, in fact not less than 108 herbal extracts. There is no specific disclosure of a mixture comprising the three herbs as employed according to the invention. The total

number of possible combinations of three herbs from 108 herbs is undoubtedly a very large number. Oppenheim simply provides no guidance or other preference to the selection of the mixture *Sambucus nigra*, *Centella asiatica* and *Echinacea purpurea*. Furthermore, the Applicants have found that the mixture of *Sambucus*, *Centella*, and *Echinacea* possesses, in addition to its therapeutic activity, another useful property: the mixture enhances the adhesiveness of a solid composition to the mucosa – see the comparative data provided in the description, illustrating the adhesive strength of a tablet containing the aforementioned herbs (as discussed in Examples 2 and 3). Thus, a considerable quantity of the herbal mixture may be effectively loaded into a solid dosage form together with excipient polymeric adhesives, wherein the herbal mixture functions both as a therapeutic agent and as an adhesive by itself, providing a dosage form which can strongly adhere to the mucosa for several hours and thereby allowing the herbs to locally exert their therapeutic effect.

In view of the above, Applicants submit that Oppenheim cannot be fairly held to disclose or suggest the combination of *Sambucus nigra*, *Centella asiatica* and *Echinacea purpurea*. *Cf. Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983) (a prior art reference must disclose all elements "as arranged in the claim"). Thus, Oppenheim's disclosure does not fairly disclose the herbal extracts as arranged in the claim.

Regarding the second feature, the Patent Office indicated that Oppenheim does not relate to the adherence of the composition to a mucosal tissue lesion in order to locally

treat the inflamed mucosa. Oppenheim is primarily directed to soft gelatin capsules which are loaded with a clear herbal extract solution. The capsule is a dosage form intended to be swallowed by the patient. Thus, the capsules described in Oppenheim are used to deliver the herbal extract systematically, through the gastrointestinal absorptive surface. Neither the capsule, nor the tablet that is mentioned in brief in page 1 of Oppenheim is expressly suggested as solid mucoadhesive composition that adheres to the mucosa. Oppenheim could not have intended to disclose or teach a solid dosage form that would stick to mucosal lesions, as such a form would prevent the active ingredients from reaching the gastrointestinal tract where they could be absorbed systemically.

Regarding the third feature, the Examiner agreed that neither the adhesive polymer of acrylic acid, nor polyvinyl pyrrolidone were taught by Oppenheim.

Due to the deficiencies in Oppenheim, the Patent Office has looked elsewhere for the remaining features combined the primary reference discussed with additional references, establishing four different obviousness rejections. Applicants, however, believe that the combined references taken together do not teach the invention (even assuming that Oppenheim were to teach the claimed combination of herbal extracts as arranged in the pending claims).

According to the first prior art combination rejection, Oppenheim was cited in combination with together with Grinstaff. Briefly, the Patent Office has taken the approach that Oppenheim teaches the mixture of herbal extracts suitable for encapsulation and Grinstaff teaches a polymeric shell suitable for encapsulating active

ingredients, where the polymeric shell can be formed from a polymer of acrylic acid and polyvinylpyrrolidone. The Patent Office then concludes that it would have been obvious to encapsulate the herbs disclosed in Oppenheim in the polymeric shell of Grinstaff.

First, it should be reemphasized that Grinstaff is not related to herbal extracts, and consequently, a person having ordinary skill in the art of therapeutic compositions of herbal extracts would not have combined the two references, and especially would not have selected a mixture of *Sambucus nigra*, *Centella asiatica* and *Echinacea purpurea* and found the unexpected adhesiveness attained by the addition of said mixture in a solid dosage form. Grinstaff, instead, relates to the *in-vivo* delivery of a biologic. (Grinstaff at 6:8-11.) Thus, at least for this reason, the two references, even when taken together, do not teach the composition and methods of the invention. There is no reason to believe that a delivery system for a biologic would be applicable to Oppenheim.

Furthermore, the combination of references cited by the Patent Office does not suggest the formulation of the herbal extracts into a solid mucoadhesive dosage form which adheres to the mucosa for treating a mucosal lesion. Like Oppenheim, Grinstaff is primarily concerned with methods for delivery of active ingredients to access the systemic circulation. To this end, the polymeric shell, which contains the active ingredient, is preferably suspended in a suitable medium. (*See* Grinstaff at 6:7-16 & 6:43-56). There is simply no teaching in (or rationale provided by) Grinstaff to select and use specifically the combination of polyacrylic acid and polyvinyl pyrrolidone for

making a solid mucoadhesive composition. In fact, the more preferred materials for making the polymeric shell are natural proteins. (*See* Grinstaff at 8:54-9:10.)

The observation made by the Patent Office, suggesting that the polymeric shell of Grinstaff can be formed from polyacrylic acid and polyvinyl pyrrolidone to give a dosage form having adhesive and non-adhesive sides, furthermore, does not take into account that in order to form the polymeric shell according to Grinstaff itself, the polymers must be chemically modified by introducing sulfur groups for the cross-linkage. (*See* Grinstaff at 9:11-20). The cross-linking is a key feature in making the polymeric shell of Grinstaff. Thus, even if a polymeric shell were to be made according to Grinstaff using polyacrylic acid and polyvinyl pyrrolidone, these polymers must necessarily be chemically altered and would contain thiol groups.

In conclusion, even if a polymeric shell described in Grinstaff would have been selected by the ordinarily skilled artisan for loading therein the specific herbal mixture recited in the pending claims, then the result would still not have been a solid mucoadhesive composition which adheres to the mucosal tissue for locally treating an inflamed mucosa. Rather, the result would have been for a delivery device for accessing the systemic circulation (which, according to Grinstaff, requires the chemical alterations). This is consistent with the observation that the straightforward way of employing the polymeric shells of Grinstaff is by means of a suspension, clearly signifying that no adhesion of a solid dosage form to the mucosa is intended by this reference.

Finally, it should be emphasized that the dosage form embodied by the polymeric shell of Grinstaff has nothing in common with the tablet claimed in claim 2. A shell is structurally and functionally different from a tablet. The tablet of claim 2 has two distinct faces: adhesive and non-adhesive; in use, the adhesive face is placed onto the mucosa, such that the non-adhesive face projects away from the site to be treated, as explained in page 4 of the specification. It almost goes without saying that a polymeric shell loaded with the active ingredient cannot be used or structured in a similar or even comparable manner.

According to the second prior art combination rejection, Oppenheim was cited together with Grinstaff and Brinkhaus. According to the Patent Office, the Brinkhaus publication teaches the application of *Centella extract* to an ulcerous lesion. It therefore appears that the reasoning for the rejection is that the Patent Office has taken the position that a person of ordinary skill in the art at the time of the invention would have presciently chosen (i) a select few active ingredients from Oppenheim, (ii) the delivery device directed to biologics from Grinstaff, and (iii) the mode of administration from the Brinkhaus paper.

Again, it is important to note that the references, even when taken together, do not teach the specific combination of *Sambucus nigra*, *Centella asiatica* and *Echinacea purpurea*, and its useful property as discussed above and as arranged in the claims. There is absolutely no teaching based on the wound healing properties of *Centella asiatica* described in Brinkhaus would lead one to expect there to be greater adhesion of a solid

mucoadhesive composition attained by the addition of a mixture of *Centella*, *Sambucus*, and *Echinacea*. It is also important to highlight that is no indication that the polymeric shell of Grinstaff (which polymeric shell is most typically delivered in suspension), is actually mucoadhesive.

In view of the deficiencies of the two references noted above, Brinkhaus cannot lead the artisan to the present invention. Brinkhaus report that *Centella asiatica* is administered orally (in the form of tablets and drops), topically (as ointment and powder) and by means of injections. (*See* Brinkhaus at 433.) There is no suggestion in the Brinkhaus reference to use, for topical application to target area treatment, the solid mucoadhesive composition of the invention. Absent the Applicants' non-obvious finding that the combination of *Sambucus*, *Centella*, and *Echinacea* enhances adhesiveness to the mucosa, there would have been no motivation or rationale to formulate the three particular herbs into a solid mucoadhesive composition which can be placed onto the mucosa to effectively accomplish the local treatment.

For at least the reasons set forth above, it is believed that the third and fourth rejections, based on the Kim and Britton, do not make up for the technical deficiencies in the Oppenheim, Grinstaff, and Brinkhaus. Moreover, Kim and Britton do not even relate to the field of herbal extracts. Kim generally relates to a therapeutic agent for osteoporosis. (Kim at [0009].) And Britton "relates to an intravaginally-dissolvable contraceptive suppository" that include a lyophilized foam and a contraceptive. (Britton at Abstract.) There is simply no reason to believe that a person of ordinary skill would

have looked to the teachings of these references to combine them with the disclosure of Oppenheim, the disclosure of Grinstaff, and the disclosure of Brinkhaus.

Although unnecessary for the patentability of all pending claims, Applicants note that inherency requires that the prior art necessary perform the claim limitations. In this regard, *Perricone v. Medicis Pharmaceutical Corp.*, 432 F.3d 1368 (Fed. Cir. 2005) is instructive. In that case, the Federal Circuit determined that a prior art composition inherently anticipated the prevention of sunburn but did not inherently anticipate the treatment of sunburn. In part, the court explained: "New uses of old products or processes are indeed patentable subject matter. *See* 35 U.S.C. § 101 (2000) (identifying as patentable 'any new and useful improvements' of a process, machine, manufacture, etc.); *In re King,* 801 F.2d 1324, 1326 (Fed.Cir.1986) (principles of inherency do not prohibit a process patent for a new use of an old structure). That principle governs in this case as well." *Perricone*, 432 F.3d at 1378. Thus, at least method claims 11-16 are patentable independently from the composition claims, because there is nothing to show that the claimed methods would have necessarily been present in the prior art.

Similarly, the rejections that rely on "routine optimization" are legally insufficient. The Office Action reasoned that it would have been obvious to combine particular disclosures from these references, then optimize that combination of isolated teachings. But case law is well established that "the discovery of an optimum value of a variable in a known process is normally obvious[, except] . . . where [1] the results of optimizing a variable, which was known to be result effective, were unexpectedly good . . . [or where]

[2] the parameter optimized was not recognized to be a result-effective variable." *In re Antonie*, 559 F.2d 618, 620 (CCPA 1977). At a minimum, the cited references do not teach that the amounts or dissolution times would be result-effective. Thus, at least claims 3, 15, and 16 are patentable independently from the claims on which they depend (which are all patentable at least for the reasons stated in this response).

All claims are in good condition for allowance. If any small matter remains outstanding (e.g., that may be resolved with an Examiner's Amendment), the Examiner is encouraged to telephone Applicants' representative. Prompt reconsideration and allowance of this application is requested.

The Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Account No. 14-1140.

Respectfully submitted,

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